REMARKS

The applicants acknowledge the withdrawal of rejections under 35 U.S.C. § 103 advanced in the previous Office action that were founded upon Kumar. Claims 1-22, 25, 28, 31, and 34-61, and 63 are pending herein as claims 23, 24, 26, 27, 29, 30 and 62 are cancelled without prejudice or disclaimer. Claims 1, 34, 38-39, and 61 have been amended, claim 63 is new, and no new matter has been added as the amendments find basis in the claims as filed and in the specification throughout (*e.g.*, page 5, lines 18-25).

Removing the term "by tumble rotation" in claim 1 renders the objection to claim 60 moot under 37 C.F.R. § 1.75(c) because claim 60 further limits the subject matter of amended claim 1. The cancellation of claim 62 also should obviate any objection under 37 C.F.R. § 1.75(c) and should obviate any rejection for double-patenting under 35 U.S.C. § 101.

With the objections rendered moot, remaining are rejections for alleged obviousness under 35 U.S.C. § 103 in view of Lang *et al.* (EP 487 774), alone and in combination with other documents. As amended claims 1 and 34 are directed to methods in which the "system includes about 20% water or organic solvent" rather than "about 20% water and/or organic solvent," it is respectfully submitted that the rejections are rendered moot as described in further detail below.

Rejection of claims over Lang alone

Claims 1-10, 12-17, 22, 25, 31, 34-44, 47-52, 56-57 and 59-60 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lang. As noted above, independent claims 1 and 34 are amended to clarify that the mixture utilized in the thermal adhesion granulation (TAG) process contains at most about 20% moisture or organic solvent. This low moisture or organic solvent content is in keeping with the specification on page 3, lines 29-30:

> Thus, the object of the present invention is to develop an alternative granulation process which utilizes considerably less water or solvent than the traditional wet granulation method (emphasis added).

The low water or solvent content is reiterated in Examples 1, 6 and 8, in which the TAG processes utilize only 5% water or 1.5% ethanol. The TAG process is not performed with mixtures having a 40% initial moisture content, for example. Thus, the "or" language in claims 1 and 34 specifies the TAG processes are performed with substantially dry mixtures having between about 0.1% and about 20% water or solvent content.

In contrast, Lang describes wet granulation, spray granulation, and spray drying processes which require comparatively large amounts of granulation fluid. These are substantially "wet" processes rather than the claimed substantially dry TAG processes. As described in detail in the supplemental amendment filed March 3, 2003, Examples I, II and III in Lang utilize 62.4%, 61.7% and 41.9% granulation fluid content, respectively, which are far higher than the initial moisture amounts claimed. Thus, Lang fails to disclose, teach or suggest granulation techniques with essentially dry mixtures.

The claimed substantially dry TAG processes offer several advantages over the substantially "wet" processes described in Lang. For example, a drying stage is unnecessary or substantially reduced for the claimed methods, whereas the vast volumes of solvent or water required for the granulation methods discussed in Lang necessitate substantial post-granulation drying steps. These additional drying steps require drying equipment which further complicates the manufacturing process and significantly increases the energy, costs, and production time. Further, the TAG processes claimed here do not require that the mixture is forced through granulation devices (*e.g.,* a sieve or impeller assembly) nor does it require that a binder solution is sprayed upon powder suspended in an air stream (*e.g.,* spray granulation or spray drying). Rather, the TAG process can be carried out by tumble rotation, as specified in claims 35 and 60, which differs from the spraying techniques discussed in Lang (described in more detail below). Lang does not teach or suggest the TAG granulation processes or these imparted advantages.

There has been some discussion during prosecution as to whether fluidized bed granulation is performed in a closed system (as advanced by the Office) or in an open system (as advanced by the applicants). The applicants respectfully maintain their position, but distinguish

the claimed TAG processes over fluidized bed granulation processes hereafter on other grounds. The following table illustrates distinguishing characteristics of each process: binder application; water or solvent usage; movement of mass across reactor system boundaries; and movement of solids within the reactor.

PARAMETER	FLUIDIZED BED GRANULATION	TAG
Binder application	Binder is first dissolved in a solution. The binder solution is then sprayed upon the excipient solids	Binder powder is dry-mixed with the other excipient solids prior to granulation.
Water or solvent usage	Significant quantities of water or solvent are utilized in a continuous spray of binder solution	No more than 20% of water or solvent is used in the process.
Movement of mass across reactor system boundaries	Solids are retained in system (reaction vessel), but air, moisture, and solvent vapors cross system boundaries	All forms of mass are retained in system (reaction vessel) during granulation, including solids, air, moisture and solvent vapor
Movement of solids within reactor	Reactor is stationary; particles move in random motion while suspended in air stream.	Reactor rotates about a horizontal axis. Particles move collectively by tumble rotation (as defined in the specifications of the application)

As illustrated in the table, one difference between the TAG processes and other conventional granulation processes such as fluidized bed granulation is illustrated by the movement of mass across the reactor system boundaries (shown in the fourth row of the table). It is the retention of all mass, specifically solvent and water vapors, which allows granulation to be possible in TAG processes with the addition of only small amounts of solvent or water.

Movement of solids within the reactor also is a distinguishing parameter between the two processes, illustrated by the last row of the table. As specified in claims 35 and 60, tumble rotation is defined in the specification as "rotation of a container about an inner horizontal axis,

or by the powder mixture mass inside the containers made to slide, roll, flow, fall or otherwise move along the inner wall of the container" (*see* specification at page 5, lines 21-23). These characteristics are not inherent to fluidized bed granulation, distinguishing that process from the TAG processes claimed herein. Accordingly, these defining characteristics of the TAG processes further discriminate the wet granulation, spray granulation and spray drying processes discussed in Lang.

Lang also fails to teach or suggest the subject matter of claims 34-55 because it does not discuss a TAG process in which excipients and active ingredients are dry-blended before water or a pharmaceutically acceptable organic solvent is added to the dry-blended mixture. Rather, the examples in Lang are directed to typical wet granulation methods in which whetted excipients individually are combined with one another and then the resulting liquid mixture is subjected to sieving and/or drying methods. Thus, Lang does not teach or suggest the processes of claims 34-55.

With regard to product by process claims 22 and 56, the TAG processes result in a granulated product having different properties than those produced by the wet techniques of Lang. For example, the present application makes it clear that the presence of excessive moisture in wet granulation processes can negatively affect ingredients in the tabletting formulation, resulting in reduced compressibility of certain excipients (*e.g.,* page 3, lines 9-19). The enhanced compressibility of products prepared by the TAG processes are evidenced by data set forth in the Example section. As described in the amendment filed March 3, 2003, the tensile strength of tables produced by the TAG processes are superior to the tensile strength prepared by the methods discussed in Lang. These surprisingly advantageous tensile strengths afforded by the TAG processes show that the granulated products are inventive over what is described in Lang. Accordingly, the product by process claims 22 and 56 are not obvious in view of Lang.

Thus, claims 1-10, 12-27, 22, 25, 31, 34-44, 47-52, 56-57 and 59-60 are not *prima facie* obvious over Lang and it is respectfully requested that this rejection be withdrawn.

Rejection of claims over Lang in combination with other documents

Certain claims were rejected as allegedly being unpatentable over Lang in view of Hughes (U.S. Patent No. 6,350,651), and it is respectfully submitted that the rejection is rendered moot by the claim amendments and cancellations. Hughes focuses upon a pharmaceutically acceptable anhydrous paratoluene sulphonic acid salt of a specific compound characterized in Formula I. While Hughes discusses formulations of this specific compound with various components and makes passing references to PVP and DCPA, the document does not discuss aspects of the claimed features lacking in Lang. Specifically, Hughes fails to discuss TAG processes in which essentially dry mixtures are formulated (*e.g.*, water or solvent contents up to about 20%) and fails to mention that the mixtures are heated in a closed system. Accordingly, the combination of Hughes and Lang does not render the claimed TAG processes and products *prima facie* obvious.

It also should be noted that Hughes does not address the subject matter of claim 61, which is directed to a method of using DCPA as an anti-caking agent to generate a finely divided powder mixture having hygroscopic PVP. Hughes discusses DCPA but does not disclose, teach or suggest methods of using DCPA as an agent that can counter the hygroscopicity and clumping tendencies of PVP. Thus, the combination of Hughes and Lang does not render claim 61 *prima facie* obvious. As Hughes alone or in combination does not teach or suggest this process, it also fails to teach or suggest the finely divided product of the process.

Certain claims also were rejected for alleged obviousness over the combination of Lang and Ansel or the combination of Lang, Ansel and Hughes, which rejections are rendered moot by the claim amendments and cancellations. Many of the claims directed to tablets, capsules and pellets have been cancelled herein without prejudice or disclaimer (*i.e.*, claims 26, 27, 29, 30, 32 and 33). For pending claims directed to tablets, capsules and pellets (*i.e.*, claims 25, 28, 31, 57, 58 and 59), Ansel fails to teach or suggest features of these claims lacking in Lang and Hughes. Specifically, the claimed products comprise the product manufactured by the TAG processes of claims 1 and 34, which are distinct from those prepared by the processes discussed in the cited

documents (*e.g.*, as indicated by surprisingly high tensile strengths described above). Because the cited documents fail to teach or suggest the products manufactured by the processes of claims 1 and 34, the claims are not rendered *prima facie* obvious by the combination of Ansel and Lang or the combination of Ansel, Lang and Hughes.

Certain claims were rejected for alleged obviousness over Lang in combination with Rudnic, and it is respectfully submitted that the rejection is rendered moot by the claim amendments and cancellations. While Rudnic mentions including crospovidone in tablet formulations, it fails to teach or suggest features lacking in the claimed TAG processes also lacking in Lang. For example, Rudnic, like Lang, fails to discuss TAG processes in which essentially dry mixtures are formulated. Accordingly, the combination of Lang and Rudnick fails to teach or suggest the claimed subject matter, and therefore, the claims are not rendered *prima facie* obvious by this combination.

CONCLUSION

It is respectfully submitted that the claim cancellations and amendments obviate the objections under 37 C.F.R § 1.75 and render moot the obviousness rejections over Lang alone or in combination with other documents. It is respectfully asserted that the obviousness rejections are rendered moot because the amended claims are directed to TAG processes involving essentially dry mixtures. These claimed processes are in stark contrast to those described in Lang and the other cited documents as they discuss substantially wet processes in which comparatively large amounts of solvents are utilized. There are several advantages associated with the essentially dry TAG processes, such as imparting surprisingly high tensile strengths to the manufactured products, which are not discussed in the cited documents. Accordingly, it is respectfully concluded that the pending claims are not *prima facie* obvious, and it is respectfully requested that the rejections be withdrawn.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 205032001200.

Respectfully submitted,

Dated: October 20, 2003 By: _____

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